REMARKS

Following entry of the above amendment, claims 8-11, 13, 15, 17-20, 22-25, 28, and 34-50 will be pending in this application, claims 14 and 16 having been canceled and new claims 47-50 added. Claims 11, 15, 43, and 45 are currently amended. Support for the amendments and new claims can be found throughout the specification and claims as originally filed, for example at page 10, lines 9-13. No new matter has been added.

Applicants thank the Examiner for acknowledging the allowability of claims 8-10, 17-19, 22-24, 28, 44, and 46 .

Specification

The specification was objected to for failing to disclose a SEQ ID NO for the amino acid sequence disclosed on page 18, line 2. Applicants respectfully point out that a sequence identifier for the sequence in question was added in an amendment dated January 14, 2002. Applicants request withdrawal of the objection.

The Office Action also requested that the specification at page 1, line 4, be amended to reflect the status of the parent 09/684,579 application. The paragraph has been amended herein to reflect that application 09/684,579 has issued as U.S. Patent No. 6,670,450.

Applicants have also amended the title of the application to "GENE INVOLVED IN MYOCYTE DIFFERENTIATION", which Applicants believe is indicative of the claims in this application.

Rejections under Section 112, first paragraph

Claims 11, 13-16, 20, 25, 34-43, and 45 have been rejected under section 112, first paragraph, for alleged lack of enablement. The Examiner's arguments in this regard are summarized and addressed below, beginning with those that pertain to claim 11 and its dependents.

Claim 11 is drawn to an isolated *nucleic acid* comprising a *strand* that hybridizes under defined conditions to a probe consisting of a defined part of SEQ ID NO:2 or the complement

thereof, where the *nucleic acid* encodes a polypeptide with a defined activity. The Office Action appears to interpret claim 11 as illogically implying that a strand that is antisense to SEQ ID NO:2 could encode such a polypeptide. In fact, the claim does not imply that the hybridizing strand itself must encode the polypeptide; rather, the hybridizing strand must simply be part of a "nucleic acid" (which of course can be double stranded) that encodes the polypeptide. Properly interpreted, the sense/antisense aspect of claim 11 does not raise any enablement issues.

A second enablement issue raised in the Office action concerns the fact that claims 14 and 16 (which depend from claim 11) state that the nucleic acid or strand can be as short as 15 nucleotides in length, a length that is allegedly inconsistent with the requirement that the nucleic acid encode a polypeptide with the defined function. Applicant does not acquiesce in this ground for rejection, but nevertheless has canceled these two dependent claims. The "at least 15 nucleotides in length" limitation appears in new claim 47, which resembles claim 11 but does not include the requirement that the nucleic acid encode a polypeptide. Utilities for the nucleic acids of claim 47 include use, e.g., as probes or primers, none of which require the nucleic acids to be long enough to encode a functional protein.

A third enablement issue raised in the Office action concerns the alleged "absence [in claim 11] of limitations regarding the sequence length over which the hybridization takes place." Applicants note that the hybridization conditions specified in the claim are high stringency conditions, and as such require a high degree of complementarity to the probe in order to produce hybridization. Further, since the sequence of the probe "consists of" nucleotides 294 through 740 of SEQ ID NO:2 or the complement thereof (i.e., there is no additional probe sequence permitted on either end of the specified part of SEQ ID NO:2), the complementarity to the probe unambiguously must be to part or all of that portion of SEQ ID NO:2. Finally, the claim requires that the nucleic acid encode a polypeptide that inhibits the differentiation of myoblasts into myotubes, a known function of the SEQ ID NO:1 protein. These limitations, taken together, ensure that the claimed nucleic acid possesses a reasonably high degree of identity to at least part of SEQ ID NO:2 and that the encoded polypeptide possesses a reasonably high degree of identity to at least part of SEQ ID NO:1. Determining whether any desired

nucleic acid falls within the claim is a simple matter of testing the parameters defined in the claim, tasks that are well within the skills of ordinary molecular biologists.

A fourth enablement issue raised in the Office action concerns claim 13, which depends from claim 11 and specifies that the amino acid sequence of the polypeptide comprises SEQ ID NO:1. Applicants can find no explanation stated in the Office action for this rejection, and request clarification. It would seem to be a routine matter to generate nucleic acids that encode SEQ ID NO:1 and that have a strand that hybridizes to the complement of the specified portion of SEQ ID NO:2, as required by the claim.

A fifth enablement issue raised in the Office action concerns the recitation in claim 15 (which previously depended from claim 11, but now depends from new claim 47) regarding inhibition of expression with the claimed antisense nucleic acid. The Examiner seems concerned with the "unpredictability" of antisense technology, inexplicably citing as an example of that unpredictability some statements about gene therapy vectors in Mountain, TIBTECH 18:119-128, 2000, as though that were relevant to a claim that says nothing whatsoever about gene therapy or vectors. See the Office action at page 5. A further passage of the Office action inexplicably asserts that "the intended uses of any pharmaceutical composition comprising an antisense nucleic acid are fraught with uncertainties," apparently failing to note that the claim says nothing about pharmaceutical compositions or pharmaceutical uses. The same passage also states, as though it were fact, that "the specification as filed does not provide any examples of the nucleic acids that inhibit the expression of a polypeptide comprising SEQ ID NO:1." This is simply not true. A working example of an antisense molecule of the invention (the antisense RNA expressed from plasmid LK444/striamin-AS) is disclosed in Examples 8 and 9 at pages 29-30 of the application and in Fig.7. Expression of this plasmid increased p53 activity in mouse fibroblasts, as an indication that endogenous striamin expression has been reduced (since striamin inhibits p53, reducing striamin expression would be expected to increase p53 activity). Regardless of the predictability or unpredictability of antisense in general, Applicants have shown it works in the context of the invention. Whether or not it can be predictably used in a

pharmaceutical context or a gene therapy context is irrelevant, since the claim is a composition claim that is not limited to either such use. As set forth in MPEP 2164.01(c):

> When a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

In view of all of the above, Applicants maintain that the rejection of claim 11 and its dependents for lack of enablement is unwarranted.

A sixth enablement issue raised in the Office action is the allegation at pages 5-6 that the various claims encompassing nucleic acids encoding a polypeptide "with at least about 60%, 80% or 95% identity to SEQ ID NO:1" or "encoding a polypeptide with 50, 30 or 10 conservative amino acid substitutions" fail to meet the enablement requirement because there "does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use" them. Applicants traverse. Each of the claims to which the Examiner apparently refers (claims 40-42 and 34-36, respectively, and perhaps claims 37-39 as well, though that isn't clear) includes a limitation that the Examiner has ignored: the encoded polypeptide "inhibits the differentiation of myoblasts into myotubes." Accordingly, it is quite apparent from the very words of the claims that a skilled artisan would know how to "use" the nucleic acids: to generate the encoded polypeptide, which can be used the same way that striamin can be used, i.e., to inhibit the differentiation of myoblasts into myotubes. The Examiner has not explained why, in his view, polypeptides having this activity cannot be so used. Likewise, Applicants do not understand why the Examiner believes that a skilled artisan would be unable to "make" the claimed nucleic acids. It is a simple matter of manipulating SEQ ID NO:2, using standard molecular biology methods, to introduce one or more mutations (e.g., claim 36 says zero to 10 conservative amino acid substitutions) at any desired site. One would certainly expect that most conservative amino acid substitutions would have little if any impact on the activity of the protein. Indeed, Applicants showed that an entire half of the striamin

protein (the amino terminal 75 residues) could be deleted wholesale without loss of the protein's p53-inhibiting activity. See Example 8 at pages 29-30, and in particular the first full sentence of page 30. While this experiment did not measure the ability of the truncated protein to inhibit the differentiation of myoblasts into myotubes, it does show that drastic alterations (down to only 50% sequence identity) can be made without affecting one particular activity of the protein. In view of that result, the alterations permitted by claims 34-42 are relatively minor ones with a high degree of expected success, provided one follows the guidance in the specification.

In support of this aspect of the rejection, the Examiner cites various references by, for example, Attwood, Skolnick et al., Metzler et al., Burgess et al., Lazar et al., and Bowie et al. to argue that even a single amino acid substitution often dramatically affects the biological activity and characteristics of a protein. Applicants agree that it is possible, at least in some cases, to abolish activity of a given protein by mutating a critical residue, as disclosed by the cited references. However, Applicants disagree that this fact means that one of ordinary skill cannot make functional analogs of SEQ ID NO:1 without undue experimentation. In fact, Bowie et al., cited by the Examiner, teaches, at page 1306, col.2, lines 12-13, that "proteins are surprisingly tolerant of amino acid substitutions." Bowie et al. cites as evidence a study carried out on the *lac* repressor. Of approximately 1500 single amino acid substitutions at 142 positions in this protein, about one-half of the substitutions were found to be "phenotypically silent": that is, had no noticeable effect on the activity of the protein (page 1306, col. 2, lines 14-17). Presumably the other half of the substitutions exhibited effects ranging from slight to complete abolishment of repressor activity. Thus, one can expect, based on Bowie et al.'s teachings, to find over half (and possibly well over half) of random substitutions in any given protein to result in mutated proteins with full or nearly full activity. These are far better odds than those at issue in *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988), in which the court said that screening many hybridomas to find the few that fell within the claims was not undue experimentation. The question is not whether it is *possible* to abolish activity with a point mutation (as the Examiner seems to believe), but rather whether one of ordinary skill can produce, without undue experimentation, mutants in which the activity is not abolished. Based on Bowie et al.'s teachings, one would predict that

even random substitution of residues in SEQ ID NO:1 will predictably result in a majority of the mutants' having the ability to inhibit the differentiation of myoblasts into myotubes. Given the information provided in the specification regarding identified characteristics of striamin, including the presence of the p53-inhibiting activity in the C-terminal half of the protein (see the above discussion) and putative phosphorylation sites (see, e.g., page 25), one of ordinary skill would know to make changes preferentially in other regions, or only conservative changes in those regions, thereby making the predictability of success even higher than in the *lac* repressor study reported by Bowie. Furthermore, the specification amply teaches how to make and test mutants (see, e.g., pages 29-33) to find those with the differentiation inhibition activity required by the claims. The Examiner's startling view that "the skilled artisan would not reasonably expect a polypeptide having anything less than 100% identity over the full length of SEQ ID NO:1 to share the same function as the polypeptide of SEQ ID NO:1" is manifestly not warranted in view of any of the references cited by the Examiner (particularly Bowie et al.), nor in view of the guidance in the specification.

Further, the Examiner's statement "Thus the recitation of percent identity language, in the absence of limitations regarding the *sequence length over which the percent identity is required;* does not allow the skilled artisan to make and use the encoding nucleic acids commensurate in scope with the instant claims without undue experimentation" (emphasis in original) is not understood. The claims reciting percent identity (claims 41-42) clearly state that the percent identity is with respect to SEQ ID NO:1, which is a sequence of 149 amino acids. One of ordinary skill would have no trouble understanding this concept. Nor would the artisan need to use "undue experimentation" in order to generate mutants that fall within these claims. Applicants have shown that as much as 50% of the SEQ ID NO:1 sequence can be deleted without affecting the p53-inhibiting activity of the protein, suggesting that generating nucleic acids that meet the relatively modest criteria of these claims (i.e., encoding polypeptides with at least 60%, 80%, or 95% identity to SEQ ID NO:1) will be readily accomplished, and certainly not "undue".

A seventh enablement issue raised by the Office action (at page 7), apparently with respect to claims 43 and 45, is the fact that "comprising" is open-ended claim language, and when applied to a claim drawn to a nucleic acid molecule, expands the scope to include additional non-disclosed nucleic acid sequences beyond the specified sequences. Applicants are uncertain as to why the Examiner believes this is a concern, nor why he has focused on claims 43 and 45 as opposed to other claims that use exactly the same "comprising" term. Using the open-ended term "comprising" to permit exactly the expansion of scope of nucleic acid claims bemoaned by the Examiner is perfectly acceptable and has never been challenged on enablement grounds by the courts, insofar as Applicants are aware. One of ordinary skill in the art would easily be able to use standard techniques to append any desired sequence to either end of a specified sequence. This is utterly routine. Thus, making any sequence that falls within either of these claims cannot possibly be considered an enablement issue. See, for example, the specification at page 31, which discloses generation of fusion proteins containing multiple histidine residues appended to residues 1-75 of SEQ ID NO:1 (as in claim 45) or to residues 76-149 of SEQ ID NO:1 (as in claim 43). Similar fusions with GFP as the fusion partner instead of poly-His are disclosed at page 32. And of course, nucleic acids encoding full length striamin (SEQ ID NO:2) and fusions thereof are yet other explicitly disclosed embodiments of claims 43 and 45. Applicants note that both the N-terminal sequence (as required by claim 45) and the C-terminal sequence (as required by claim 43) were demonstrated to possess the functional activity of binding to p53 that is required by both claims, as amended. See the specification at page 32. The Examiner's stated fear that "the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claims and consequently would not know how to make them" does not comport with reality. Starting with the portion of SEQ ID NO:2 specified in claim 43 or 45, the artisan can imagine (i.e., "know the identity of") and then readily make any number—reasonable or not—of fusion proteins that he/she wishes, no "trial and error" required. Since the minimal sequence required by each claim possesses the specified activity, one would expect longer variants including that minimal sequence also to possess it.

Nor should the "comprising" language of these claims raise concerns about the "how to use" aspect of the enablement requirement. Applicants have demonstrated a few uses for the claim 43 and 45 nucleic acids with appended sequences, as described at pages 31-32. Other uses would be readily apparent to the person of ordinary skill, based on uses for fusion proteins well known in the art (e.g., to facilitate purification, precipitation, or assaying). And as stated above, the variants would in general all be expected to retain the stated activity of the minimal sequence. As the Examiner is well aware, and as the text from the MPEP quoted above makes clear, a single use is sufficient to establish enablement under U.S. law. A rejection of claims 43 and 45 for lack of enablement is therefore entirely inappropriate.

Claims 43 and 45 were also rejected under section 112, first paragraph, for alleged lack of written description. Applicants traverse this rejection. There is no question the specification shows that Applicants were in possession of the full scope of the claimed inventions. Examples 10 and 11 of the specification describe the construction of various polypeptides comprising residues 76 through 149 of SEQ ID NO:1 (as specified in claim 43) or residues 1 through 75 of SEQ ID NO:1 (as specified in claim 45). All of these polypeptides were shown to bind to p53, as required by both claims (as amended). It is clear from the specification that any sequence could be appended to either end of either sequence, as desired. This is not a situation such as in Fiers (cited by the Examiner), where the claim was written in functional terms and no sequence was provided. Here, the claims both specify a particular, defined minimal sequence.[1] Since "comprising" is an accepted term to use in claims, and is no more open-ended in claims 43 and 45 than in any other claim in this or any other field, Applicants are at a loss to understand why the Examiner has decided that it creates a "written description" issue in this particular situation. It does not.

In view of the above arguments, Applicants submit that claims 11, 13, 15, 20, 25, 34-43, and 45, as well as newly added claims 47-50, are fully enabled and described by the specification, and request confirmation of such by the Examiner.

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[1] The argument at page 9 of the Office action that "a description of nucleic acid sequences by functional language in the absence of a structure is not considered sufficient to show possession of the claimed invention" suggests that the Examiner either wrote that without looking at the claims, or imagines that a limitation regarding a specific sequence (such as in claims 43 and 45) is not "structure". Regardless, it is patently inappropriate.

Applicants respectfully request clarification of the Examiner's comment at page 10 regarding a probe purportedly disclosed as SEQ ID NO:95 in US Patent 6,458,533. It appears that this patent contains only 32 sequences. Consequently, Applicants have been unable to confirm whether any sequence within this patent bears the degree of similarity to Applicants' SEQ ID NO:2 alleged by the Examiner.

Applicants note the Examiner's comment on page 2 regarding the information disclosure statement filed December 1, 2003. The references that the Examiner has refused to consider were in fact all submitted with the parent application, USSN 09/684,579, now issued as U.S. patent No. 6,670,450. These references are supposedly available to the Examiner from the parent application's file. Thus, submission of new copies should be unnecessary. On the assumption that the references are in fact lost from the parent application's file, Applicants resubmitted copies of the reference and the form PTO-1449 on November 18, 2005.

Enclosed is a Petition for Extension of Time, along with the required fee. Also enclosed is a check for excess claim fees. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14875-066002.

Respectfully submitted,

Date: 1/6/06

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